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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,623	04/30/2001	Sudhir Agrawal	47508.528	2601

32254 7590 06/17/2003

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EXAMINER	
MCINTOSH III, TRAVISS C	
ART UNIT	**PAPER NUMBER**
1623	14

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application N .	Applicant(s)	
	09/845,623	AGRAWAL ET AL.	
	Examin r	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE f this communicati n appears n the cover she t with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed March 31, 2003 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1-17 have been canceled.

Claims 18, 21 and 24 have been amended.

New claims 25-27 have been added.

Remarks drawn to rejections of Office Action mailed December 23, 2002 include:

Claim objections: which have been overcome by applicant's amendments.

112 2nd paragraph rejections: which have been overcome by applicants' amendments.

102(b) rejection: which has been overcome by applicant's amendments.

An action on the merits of claims 18-27 is contained herein below.

The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 18-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 26 are drawn to compounds which may be "substituted" or "modified", but there is no identification on how applicant intends to "substitute" or "modify" the compounds

in the claims. In the absence of the identity of moieties which are intended to be substituted or modified, thus altering an art recognized chemical core, described structurally or by chemical name, the identity of "substituted" or "modified" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" or "modified" without defining what is to be "substituted" or "modified" are not described sufficiently to distinctly point out that which applicant intends as the invention.

Claim 18 is indefinite wherein the claim reads "... a compound comprising a CpG dinucleotide and an immunomodulatory moiety, selected from the group consisting of ...". It is unclear if the Markush group that follows is defining the dinucleotides or the immunomodulatory moiety. Removing the comma at the position: "immunomodulatory moiety, selected from" would be seen as a more favorable way to set forth that which applicants intend.

Claim 23 is indefinite wherein it is unclear if the step of administering the adjuvant is an additional step that is to be administered separately, or if the adjuvant is intended to be administered with the CpG/immunomodulatory/vaccine. Clarity is respectfully requested.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hutcherson et al. (US Patent 5,663,153).

The claims of the instant invention are drawn to a method for inducing an immune response in a mammal (human) comprising administering a compound comprising a CpG dinucleotide (wherein G is guanosine, 7-deazaguanosine, or inosine) and an immunomodulatory moiety (an abasic nucleoside, a 1,3-propanediol linker, or a modified base-containing nucleoside) wherein the compound has a greater immunostimulatory effect than the same

compound lacking the immunomodulatory moiety. Administration is parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal wherein dosage attains a blood level of oligonucleotide from about 0.01 micromolar to 10 micromolar and wherein the dosage is about 0.1 mg per patient per day to about 200 mg per kg body weight per day. The compound may additionally be administered in combination with a vaccine and/or an adjuvant.

Hutcherson et al. disclose a method of stimulating a local immune response in cells or tissues by administering an oligonucleotide analog having at least one phosphorothioate bond to the cells or tissues wherein the phosphorothioate analogs have shown to stimulate a local immune response (an immunomodulatory moiety) in animals and humans (column 5, lines 25-30). Examples of the oligonucleotide sequences which contain the immunomodulator are SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, disclosed in sequence listing in columns 15-16, all of which contain the CpG dinucleotide sequence. The sequences of Hutcherson et al. induced an immune response (IL-1α) when the immunomodulator was present (P=S moiety included) and did not when there was no immunomodulator present (P=O moiety included) (column 10, table 1). The composition of Hutcherson et al. is disclosed as being capable of being administered topically (ophthalmically, vaginally, rectally, intranasally), intralesionally, orally, by inhalation, or parenterally (column 8, lines 8-23). The compositions of Hutcherson et al. enhance the humoral response at a dosage of about 3.3 mg per kg body weight per day (column 14, lines 13-15) and concentrations of approximately 1 micromolar are therapeutically effective (column 12, lines 13-15). Further it is noted that Hutcherson et al. disclose that unmethylated CpG dinucleotides induce B-cell activation (column 4, lines 38-40) and that the oligonucleotides may have altered sugar moieties and altered base units (column 6, line 63 – column 7 line 19). It is

noted that Hutcherson et al. do not specifically disclose the CpG sequence with the altered base modifications (as claimed in the instant as an abasic nucleoside or a modified base-containing nucleoside), but they do indeed contemplate these modifications to increase the immune response.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the CpG oligonucleotide of Hutcherson et al. with the modified base containing nucleosides because they contemplate the use of these modified analogs. One would be motivated to use these various analogs because Hutcherson et al. teach that various modifications may be made to increase the immune stimulation by enhancing uptake, stability, affinity, or other features of the oligonucleotide (column 7, lines 5-10).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh III
June 16, 2003